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Synthesis of a novel class of sulfonium ions as potential inhibitors of UDP-galactopyranose mutase ☆

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Abstract—Two sulfonium salts of 1,4-anhydro-4-thio-D-galactitol, with structures related to the known sulfonium salt glycosidase inhibitor, salacinol, have been synthesized as potential inhibitors of UDP-galactopyranose mutase. The synthetic strategy relies on the alkylation reaction of 1,4-anhydro-2,3,5,6-tetra-*O*-benzyl-4-thio-D-galactitol at the sulfur atom with 2,4-*O*-benzylidene-D- or -L-erythritol-1,3-cyclic sulfate. In each case, the reaction proceeded stereoselectively to yield only one stereoisomer at the stereogenic sulfur atom. The effect of the polar solvent, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), in promoting high-yielding reactions is highlighted. The target compounds are then obtained by hydrogenolysis.
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Keywords: Galactofuranose; UDP-Galactopyranose mutase inhibitors; Salacinol analogues; Sulfonium salt

1. Introduction

Galactose is found to occur mostly in the pyranose form in Nature; the rare furanose form only exists in microorganisms such as bacteria,[1,2] protozoa,[3] and fungi[4] and has never been found in mammalian cells.[5] Thus, for example, Gal*f* is present in lipopolysaccharides (LPS) in the outer membrane of Gram-negative bacteria, in various capsular or extracellular polysaccharides in both Gram-negative and Gram-positive bacteria,[5,6] and as constituents of the oligosaccharide core of both the glycoinositolphospholipid (GIPL) and lipopeptidophosphoglycan (LPPG) of *Trypanosoma cruzi*, and the lipophosphoglycan (LPG) of *Leishmania* species.[7–11] Galactofuranosyl residues also play important roles in pathogenic mycobacteria such as *Mycobacterium tuberculosis* and *M. leprae*.[12,13] In addition, 'atypical mycobacteria', including the *M. avium* complex, cause opportunistic infections in immunologically compromised individuals such as AIDS patients.[13] The recognition that D-galactofuranose (D-Gal*f*) residues play crucial roles in survival and infectivity of pathogens has led to increased activity in developing therapeutic strategies.

The sugar donor for galactofuranosyl residues is UDP-Gal*f*,[14,15] which is produced in turn from UDP-Gal*p*. The interconversion of UDP-Gal*p* and UDP-Gal*f* is catalyzed by the enzyme UDP-galactopyranose mutase (Scheme 1).[15–17] The reaction has been proposed to proceed via a 1,4-anhydro-D-galactopyranose species (Scheme 1), based on evidence that the anomeric C–O bond is broken during the reaction.[18,19] Evidence for the active involvement of the coenzyme FAD in controlling the catalytic efficiency of the enzyme has also been provided,[20,21] and a study of the inactivation of the enzyme with UDP-3-deoxy-3-fluoro-Gal*f* has suggested the possible involvement of a covalent intermediate.[21] Recent evidence suggests that the ring contraction reaction might be driven by attack of OH-4 at C-1 of a glycosyl C-1 radical intermediate with concomitant cleavage of the C-1–O-5 bond (Scheme 1).[22] We note, however, that the mechanisms proposed to date are difficult to reconcile with the findings that UDP-4-deoxy-4-fluoro-Gal*p* does not inhibit the reaction of

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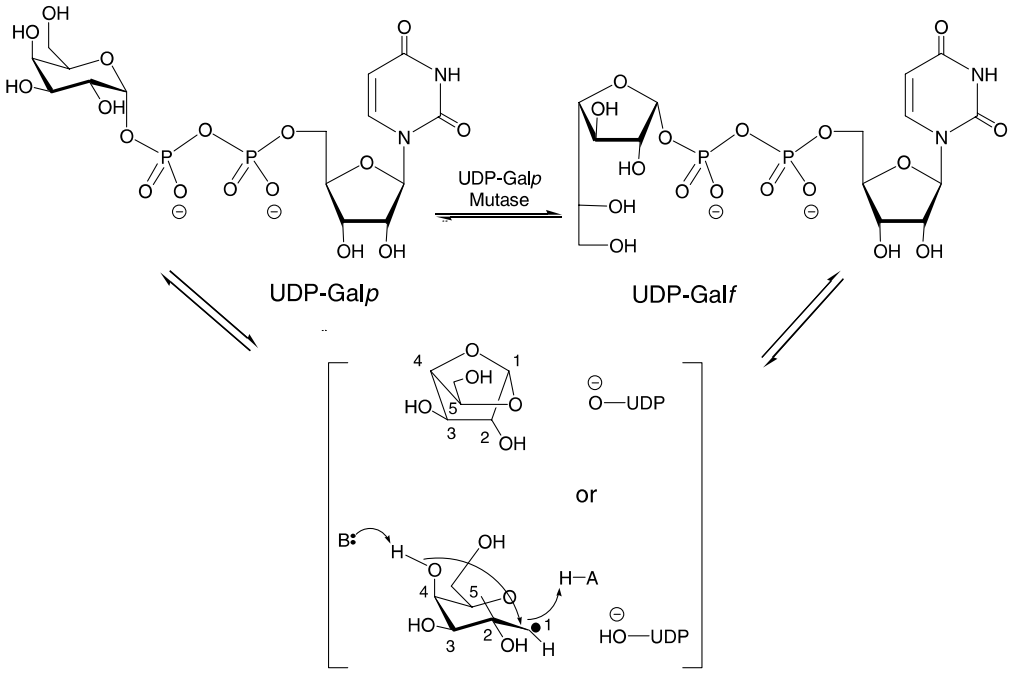
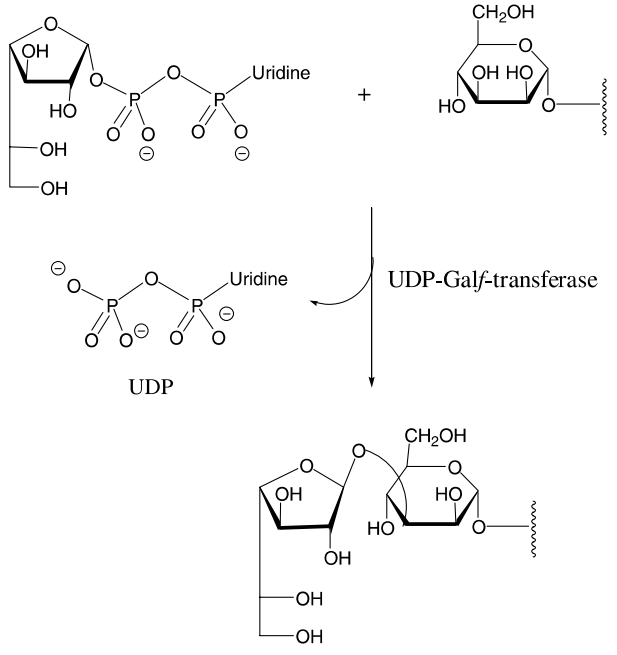


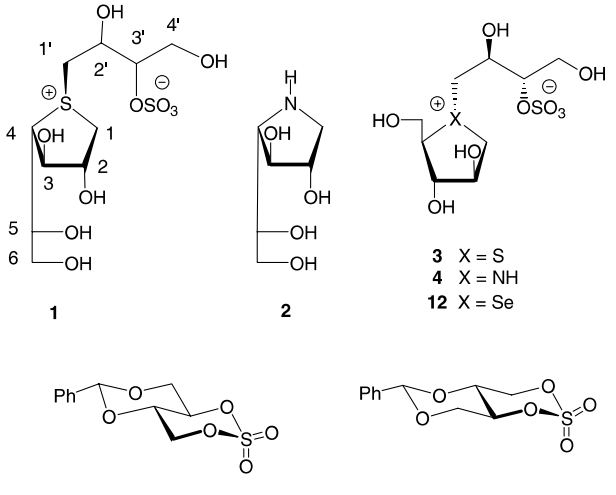
Scheme 1.

UDP-galactopyranose mutase in the direction pyranose to furanose.[23] UDP-Gal*f* then serves as a donor in glycosylation reactions catalyzed by UDP-Gal*f* transferase (Scheme 2).[24] Thus, one can envisage strategies to block the incorporation of Gal*f* into oligosaccharides that comprise blocking the action of either UDP-galactopyranose mutase or UDP-galactofuranosyl transferase.



Scheme 2.

We propose that 4-thio Gal*f* sulfonium salts **1** could be potential inhibitors of UDP-galactopyranose mutase, given that 1,4-dideoxy-1,4-imino-D-galactitol (**2**)[25] has been shown to inhibit the enzyme.[26] We argue that the protonation of the nitrogen atom in the active site provides electrostatic stabilization with carboxylate residues, and that the permanent positive charge on the sulfonium ion would serve to mimic this interaction. There is precedent for such mimicry with glycosidase enzymes, namely the glycosidase inhibitory activities of salacinol (**3**)[27–29] and the corresponding nitrogen analogue, ghavamiol (**4**).[30] We reasoned further that the biologically important side chain of salacinol containing an internal sulfate counterion would be advantageous in



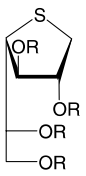
stabilizing the compound, as is the case with salacinol (**3**). We describe here the synthesis of 4-*S*-galactitol sulfonium salt derivatives **1**, based on the structure of salacinol (**3**), as potential inhibitors of UDP-galactopyranose mutase.

2. Results and discussion

Retrosynthetic analysis indicated that the target compounds could be synthesized by alkylation on the ring heteroatom of a 1,4-anhydro-4-thiogalactitol derivative (Scheme 3). The compounds for alkylation could either be the open-chain sulfate or the cyclic sulfate derivatives.[29,30] We proposed the use of cyclic sulfate derivatives as alkylation reagents, specifically 2,4-*O*-benzylidene-D- (**5**) and L- (**6**) erythritol-1,3-cyclic sulfates.[29,30]

Methyl α-D-glucopyranoside was converted to 1,2,3,5,6-penta-*O*-acetyl-4-thio-α-D-galactofuranose, as described previously.[31–33] The anhydrogalactitol derivative was then synthesized as follows. A deoxygenation reaction was carried out by reductive deacetylation using trimethylsilyl (TMS) triflate and triethylsilane at room temperature, as described for the synthesis of anhydroalditols,[34] to produce the 1,4-anhydro-4-thiogalactitol compound **7**, in 63% yield. The presence of the adjacent acetate group at C-2 presumably facilitates the deoxygenation process by stabilizing the thiacarbenium ion intermediate.[35]

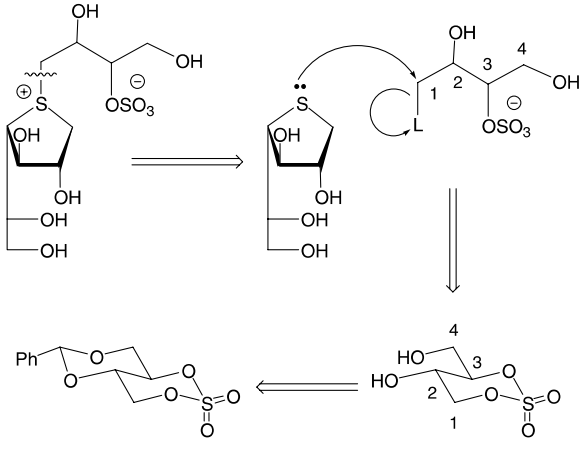
With the 1,4-anhydro-4-thio-galactitol compound **7** in hand, the key coupling reaction was then attempted. The effect of protecting groups, or the lack thereof, on the anhydrogalactitol moiety was examined. The deprotected galactitol **8** was obtained from **7** by methanolysis, and the benzylated galactitol **9** was synthesized from compound **8**, using NaH and benzyl bromide. Compounds **7**–**9** were then investigated in reactions with 2,4-*O*-benzylidene-D-erythritol 1,3-cyclic sulfate **5**. Reaction of tetra-*O*-acetyl galactitol **7** with the cyclic sulfate **5** in acetone containing potassium carbonate at 55 °C for 2 days led to no reaction. The reaction in DMF instead of acetone also failed because of the opening of the cyclic sulfate by acetate ion released from compound **7**. The reaction of the deprotected galactitol compound **8** with the cyclic sulfate **5** in DMF at 70 °C was also not successful and produced several components. Therefore, the coupling reaction was next attempted with tetra-*O*-benzyl-D-galactitol **9**.



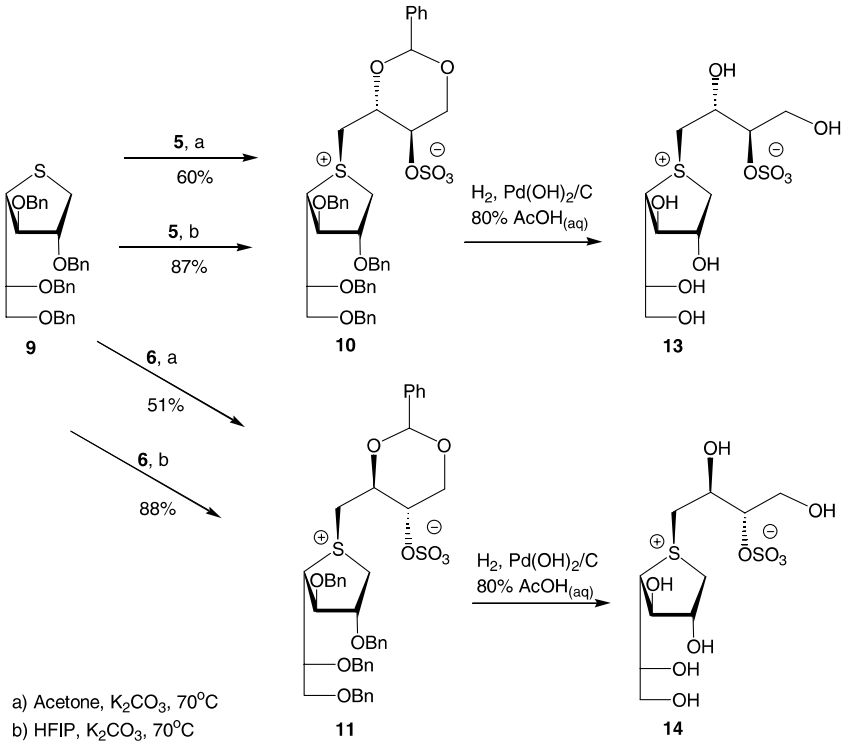
7 R = Ac
8 R = H
9 R = Bn

The reaction was first attempted in acetone at a concentration of 100 mg/mL of compound **9**. The reaction proceeded, but the yield was not satisfactory. Therefore, the reaction was attempted again at a concentration of 200 mg compound **9** in 0.5 mL of acetone. Under these reaction conditions, the reaction proceeded reasonably well to give compound **10** in 60% yield, indicating the need for extremely concentrated reaction mixtures. The same reaction conditions were used for the coupling reaction of compound **9** and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**6**) to give the diastereomeric compound **11** in 50% yield (Scheme 4). The coupling reactions proceeded stereoselectively, and in each case, only one isomer at the stereogenic sulfur atom was isolated. We had previously shown that the polar solvent, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), had a spectacular effect in promoting analogous reactions for the synthesis of salacinol **3**[36] and its selenium congener, blintol **12**.[37] We reasoned that the higher yields were due to better solvation by HFIP of the polar transition states for the reactions and the adducts relative to the neutral reactants. We therefore tested HFIP as a solvent for the coupling reaction described here. The reaction of the thioether **9** with the cyclic sulfate **5** in HFIP was much faster and proceeded in excellent yield (88%) to stereoselectively give **13**. Similarly, a dramatic increase in yield was observed for the reaction of the thioether **9** with the cyclic sulfate **6** in HFIP to give **14** (87%).

Compounds **10** and **11** were completely characterized by 2D NMR techniques and microanalysis. Deprotection of **10** and **11** was accomplished with $Pd(OH)_2/C/H_2$ in aqueous 80% acetic acid to effect the hydrogenolytic cleavage of the benzyl and benzylidene groups, and gave **13** and **14** in yields of 84% and 96%, respectively (Scheme 4). Compounds **13** and **14** were also completely characterized by 2D NMR techniques (see figures,



Scheme 3.



Scheme 4.

Supplementary Data section). The stereochemistry at the stereogenic sulfur atom in **13** and **14** was confirmed by NOESY correlations. Thus, a correlation between H-1′ and H-4 for each isomer confirmed the *trans* relationship between the erythritol side chain and the C-4 substituent on the anhydrogalactitol moiety. The barrier to inversion at the sulfonium center must be substantial since no epimerization was observed in these or related compounds.[29,38] The target compounds **13** and **14** will be tested for inhibition of UDP-galactopyranose mutase.

3. Experimental section

3.1. General

Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Autopol II automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer at 400.13 and 100.6 MHz, for proton and carbon, respectively. Chemical shifts are given in ppm downfield from TMS for those spectra measured in $CDCl_3$ or CD_3OD and from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those spectra measured in D_2O. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. All assignments were confirmed with the aid of two-dimensional ^{1}H/^{1}H (COSYDFPT), ^{1}H/^{13}C (INVBTP), ^{1}H (NOESYTP), and ^{1}H (MLEVTP) experiments using standard Bruker pulse programs. Processing of the spectra was performed with standard UXNMR (Bruker) and WINNMR software. Zero filling of the acquired data (512 t_1 values and 2K data points in t_2) led to a final data matrix of 1K × 1K ($F_1 \times F_2$) data points. MALDI-TOF mass spectra were obtained for samples in a 2,5-dihydroxybenzoic acid matrix using a PerSeptive Biosystems Voyager-DE instrument. High-resolution mass spectra were LSIMS (Fab), and were run on a Kratos Concept H double-focusing mass spectrometer at 10,000 RP. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with E. Merck Silica Gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light and/or sprayed with a solution containing 1% $Ce(SO_4)_2$ and 1.5% molybdic acid in 10% aq H_2SO_4, and heated. Compounds were purified by flash column chromatography on E. Merck Kieselgel 60 (230–400 mesh). Solvents were distilled before use and were dried, as necessary, by literature procedures. Solvents were evaporated under reduced pressure and below 50 °C.

3.2. 1,4-Anhydro-2,3,5,6-tetra-*O*-acetyl-4-thio-D-galactitol 7

1,2,3,5,6-Penta-*O*-acetyl-4-thio-α-D-galactofuranose (4.72 g, 12.0 mmol) was dissolved in CH_3CN (70 mL). TMSOTf (4.4 mL, 24.3 mmol) was added to the reaction mixture, followed by the addition of freshly distilled

Et_3SiH (5.7 mL, 35.7 mmol). The reaction mixture was kept at room temperature under nitrogen for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with water (3×50 mL) and satd aq $NaHCO_3$ (3×50 mL), then dried over $MgSO_4$. The solvent was removed, and the product was purified by column chromatography (8:3 toluene–hexanes) as a colorless syrup (2.63 g, 63%). $[\alpha]_D$ −5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.34–5.30 (2H, m, H-2, H-3), 5.28 (1H, ddd, $J_{4,5}$ 7.6, $J_{5,6b}$ 6.3, $J_{5,6a}$ 3.7 Hz, H-5), 4.43 (1H, dd, $J_{6a,6b}$ 12.0, $J_{5,6a}$ 3.7 Hz, H-6a), 4.08 (1H, dd, $J_{6a,6b}$ 12.0, $J_{5,6b}$ 6.3 Hz, H-6b), 3.53 (1H, dd, $J_{3,4}$ 4.3, $J_{4,5}$ 7.6 Hz, H-4), 3.22 (1H, dd, $J_{1a,1b}$ 11.8, $J_{1a,2}$ 4.9 Hz, H-1a), 2.91 (1H, dd, $J_{1a,1b}$ 11.8, $J_{1b,2}$ 5.2 Hz, H-1b), 2.11, 2.10, 2.07, 2.05 (12H, 4s, $COOCH_3$); ^{13}C NMR ($CDCl_3$): δ 170.49, 170.03, 169.94, 169.59 ($4COOCH_3$), 77.80, 77.62 (C-2, C-3), 70.80 (C-5), 63.78 (C-6), 50.23 (C-4), 32.63 (C-1), 20.86, 20.81, 20.67 ($4COOCH_3$); MALDI-TOF MS: *m*/*e* 371.295 (M+Na). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79. Found: C, 48.41; H, 5.79.

3.3. 1,4-Anhydro-4-thio-D-galactitol 8

Compound **7** (2.58 g, 7.41 mmol) was dissolved in MeOH (30 mL), and 1 M NaOMe (2 mL) was added. The reaction mixture was kept at room temperature under nitrogen overnight. Then, Rexyn-101 (H^+) ion-exchange resin was added to the reaction mixture until the pH was ~5. The resin was removed by filtration, and the filtrate was dried over $MgSO_4$, and concentrated. Column chromatography (16:2:1 EtOAc–MeOH–H_2O) afforded pure syrupy compound, which crystallized later on storage (1.27 g, 95%), mp 71–72 °C. $[\alpha]_D$ −75° (*c* 0.3, H_2O); ^1H NMR (D_2O): δ 4.14 (1H, ddd, $J_{1b,2}$ 8.4, $J_{1a,2}$ 7.5, $J_{2,3}$ 6.4 Hz, H-2), 3.94–3.88 (2H, m, H-3, H-5), 3.56 (1H, dd, $J_{6a,6b}$ 11.8, $J_{6a,5}$ 4.7 Hz, H-6a), 3.50 (1H, dd, $J_{6a,6b}$ 11.8, $J_{6b,5}$ 7.0 Hz, H-6b), 3.25 (1H, m, H-4), 2.95 (1H, dd, $J_{1a,1b}$ 10.8, $J_{1a,2}$ 7.5 Hz, H-1a), 2.68 (1H, dd, $J_{1a,1b}$ 10.8, $J_{1b,2}$ 8.4 Hz, H-1b); ^{13}C NMR (D_2O): δ 80.55 (C-3), 79.08 (C-2), 73.44 (C-5), 66.79 (C-6), 52.73 (C-4), 33.56 (C-1); MALDI-TOF MS: *m*/*e* 202.804 (M+Na). Anal. calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71. Found: C, 39.95; H, 6.78.

3.4. 1,4-Anhydro-2,3,5,6-tetra-*O*-benzyl-4-thio-D-galactitol 9

Compound **8** (0.86 g, 4.77 mmol) was dissolved in dried, freshly distilled DMF (25 mL), the reaction flask was cooled with an ice bath, then NaH (60% in mineral oil, 0.86 g, 21.5 mmol) was added slowly into the solution. Benzyl bromide (2.7 mL, 22.7 mmol) was added dropwise into the reaction mixture. The ice bath was then removed, and the reaction mixture was stirred at room temperature overnight under nitrogen. The reaction mixture was diluted with EtOAc (30 mL) and washed with water (3×30 mL), dried over $MgSO_4$, and then concentrated. The crude material was purified by column chromatography (9:1 hexanes–EtOAc) to obtain the title compound **9** as a syrup (1.91 g, 74%). $[\alpha]_D$ −34° (*c* 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 7.38–7.21 (20H, m, Ar), 4.69 and 4.55 (2H, 2d, $J_{A,B}$ 11.6 Hz, CH_2Ph), 4.65 and 4.41 (2H, 2d, $J_{A,B}$ 11.6 Hz, CH_2Ph), 4.60 and 4.54 (2H, 2d, $J_{A,B}$ 11.9 Hz, CH_2Ph), 4.18 (1H, ddd, $J_{1b,2}$ 7.0, $J_{1a,2}$ 5.6, $J_{2,3}$ 5.8 Hz, H-2), 4.08 (1H, dd, $J_{2,3} = J_{3,4} = 5.8$ Hz, H-3), 3.81 (1H, q, $J_{4,5} = J_{5,6a} = J_{5,6b} =$ 5.4 Hz, H-5), 3.59 (1H, dd, $J_{6a,6b}$ 10.2, $J_{5,6a}$ 5.4 Hz, H-6a), 3.56 (1H, dd, $J_{6a,6b}$ 10.2, $J_{5,6b}$ 5.4 Hz, H-6b), 3.53 (1H, dd, $J_{3,4}$ 5.8, $J_{4,5}$ 5.4 Hz, H-4), 2.99 (1H, dd, $J_{1a,1b}$ 10.8, $J_{1a,2}$ 5.6 Hz, H-1a), 2.86 (1H, dd, $J_{1a,1b}$ 10.8, $J_{1b,2}$ 7.0 Hz, H-1b); ^{13}C NMR ($CDCl_3$): δ 138.40, 138.28, 138.07, 138.02 ($4C_{ipso}$), 128.43–127.62 ($20C_{Ar}$), 85.30 (C-2), 84.36 (C-3), 78.23 (C-5), 73.40, 72.99, 72.17, 71.84 ($4CH_2Ph$), 71.65 (C-6), 50.66 (C-4), 31.45 (C-1). Anal. calcd for $C_{34}H_{36}O_4S$: C, 75.52; H, 6.71. Found: C, 75.62; H, 6.65.

3.5. 1,4-Anhydro-2,3,5,6-tetra-*O*-benzyl-4-[(*R*)-[(2*R*,3*R*)-2,4-benzylidenedioxy-3-(sulfooxy)butyl]sulfoniumylidene]-D-galactitol inner salt 10

3.5.1. Reaction in acetone. Compound **9** (0.96 g, 1.78 mmol) was dissolved in acetone (2 mL), and 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic sulfate **5**[17] (580 mg, 2.13 mmol), and K_2CO_3 (50 mg) were added. The reaction mixture was stirred at 70 °C under nitrogen overnight. The reaction mixture was then filtered and concentrated. The crude product was purified by column chromatography first with CH_2Cl_2 to elute the nonpolar starting materials, then (19:1 CH_2Cl_2–MeOH) to obtain the title compound **10** (0.86 g, 60%). The syrupy product was crystallized and recrystallized from CH_2Cl_2/hexanes.

3.5.2. Reaction in HFIP. Compound **9** (200 mg, 0.37 mmol) was dissolved in HFIP (0.5 mL), and 2,4-*O*-benzylidene-D-erythritol 1,3-cyclic sulfate **5** (130 mg, 1.2 equiv), and K_2CO_3 (10 mg) were added. The reaction mixture was stirred at 70 °C under nitrogen overnight. The reaction mixture was then filtered and concentrated. The crude product was purified by column chromatography, first with CH_2Cl_2 to elute the nonpolar starting materials, then with (19:1 CH_2Cl_2–MeOH) to obtain the title compound **10** (260 mg, 87%) as a white foam, mp 65–66 °C. $[\alpha]_D$ −8° (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 7.46–7.09 (25H, m, Ar), 5.37 (1H, s, $CHPh$), 4.65 (1H, ddd, $J_{2',3'} = J_{3',4'ax} = 9.7$, $J_{3',4'eq}$ 5.4 Hz, H-3′), 4.56–4.50 (1H, m, H-2), 4.53–4.47 (1H, m, H-4′eq), 4.47–4.24 (8H, m, CH_2Ph), 4.31–4.29 (1H, m, H-3), 4.30–4.24 (1H, m, H-1′a), 4.17–4.10 (2H, m, H-2′, H-4), 4.06 (1H, dd, $J_{1'b,1'a}$ 13.5, $J_{1'a,2'}$ 2.2 Hz, H-1′b), 3.93 (1H, dd, $J_{1a,1b}$ 13.5,

$J_{1b,2}$ 1.6 Hz, H-1a), 3.75 (1H, dd, $J_{1a,1b}$ 13.5, $J_{1b,2}$ 3.8 Hz, H-1b), 3.71–3.68 (2H, m, H-4′ax, H-5), 3.37 (1H, dd, $J_{6a,6b}$ 10.8, $J_{6a,5}$ 3.8 Hz, H-6a), 3.32 (1H, dd, $J_{6a,6b}$ 10.8, $J_{6b,5}$ 4.3 Hz, H-6b); ^{13}C NMR ($CDCl_3$): δ 137.06–136.02 ($5C_{ipso}$), 129.17–126.56 ($25C_{Ar}$), 101.71 (*C*HPh), 83.23 (C-3), 82.59 (C-2), 76.45 (C-2′), 74.47 (C-5), 73.53, 73.03, 72.23, 72.20 ($4CH_2$Ph), 69.69 (C-4), 69.42 (C-6), 69.27 (C-4′), 66.46 (C-3′), 49.11 (C-1′), 47.10 (C-1); MALDI-TOF MS: *m/e* 813.117 (M). Anal. calcd for $C_{45}H_{48}O_{10}S_2$: C, 66.48; H, 5.95. Found: C, 66.47; H, 5.91.

3.6. 1,4-Anhydro-2,3,5,6-tetra-*O*-benzyl-4-[(*R*)-[(2*S*,3*S*)-2,4-benzylidenedioxy-3-(sulfooxy)butyl]sulfoniumylidene]-D-galactitol inner salt 11

3.6.1. Reaction in acetone. Compound **9** (0.496 g, 0.92 mmol) was dissolved in acetone (1 mL) and 2,4-*O*-benzylidene-L-erythritol 1,3-cyclic sulfate **6**[17] (0.31 g, 1.13 mmol), and K_2CO_3 (25 mg) were added. The reaction was carried out as described for the case of **10**. The title compound **11** (0.38 g, 51%) was obtained as a white foam.

3.6.2. Reaction in HFIP. Compound **9** (100 mg, 0.18 mmol) was dissolved in HFIP (1 mL), and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **6** (70 mg, 1.2 equiv), and K_2CO_3 (10 mg) were added. The reaction was carried out as described for the case of **10**. The title compound **11** (132 mg, 88%) was obtained as a white foam. $[\alpha]_D$ +10° (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.36–7.05 (25H, m, Ar), 5.10 (1H, s, C*H*Ph), 4.61 (1H, dd, $J_{4'eq,4'ax}$ 11.0, $J_{3',4'eq}$ 5.5 Hz, H-4′eq), 4.48 and 4.37 (2H, 2d, $J_{A,B}$ 11.8 Hz, CH_2Ph), 4.45 and 4.35 (2H, 2d, $J_{A,B}$ 10.7 Hz, CH_2Ph), 4.45–4.34 (6H, m, CH_2Ph, H-3′, H-1′a, H-2, H-4), 4.28 and 4.21 (2H, 2d, $J_{A,B}$ 12.0 Hz, CH_2Ph), 4.23 (1H, m, H-3), 4.15 (1H, ddd, $J_{1',2'} = J_{2',3'} = 7.9$, $J_{1',2'}$ 2.5 Hz, H-2′), 4.11 (1H, dd, $J_{1a,1b}$ 13.4, $J_{1a,2}$ 2.1 Hz, H-1a), 3.73–3.64 (3H, m, H-1′b, H-1b, H-5), 3.61 (1H, dd, $J_{4'eq,4'ax} = J_{3',4'ax} = 11.0$ Hz, H-4′ax), 3.31 (1H, dd, $J_{6a,6b}$ 10.7, $J_{5,6a}$ 3.8 Hz, H-6a), 3.28 (1H, dd, $J_{6a,6b}$ 10.7, $J_{5,6b}$ 4.7 Hz, H-6b); ^{13}C NMR ($CDCl_3$): δ 136.94, 136.46, 136.06, 135.99 ($5C_{ipso}$), 129.22–126.47 ($25C_{Ar}$), 101.27 (*C*HPh), 82.57 (C-2), 82.38 (C-3), 76.75 (C-2′), 74.91 (C-5), 73.41, 73.06, 72.03, 71.83 ($4CH_2$Ph), 69.54 (C-4′), 68.99 (C-6), 68.86 (C-4), 67.88 (C-3′), 46.93 (C-1′), 46.79 (C-1); MALDI-TOF MS: *m/e* 813.34 (M). Anal. calcd for $C_{45}H_{48}O_{10}S_2$: C, 66.48; H, 5.95. Found: C, 66.39; H, 5.87.

3.7. 1,4-Anhydro-4-[(*R*)-[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]sulfoniumylidene]-D-galactitol inner salt 13

Compound **10** (200 mg, 0.25 mmol) was dissolved in 80% AcOH (6 mL), then $Pd(OH)_2$/C (120 mg) was added to the solution. The reaction mixture was stirred at room temperature in a stainless steel pressure bomb under 120 psi hydrogen for 3 days. The reaction mixture was filtered through Celite, and then MeOH was used to wash the Celite. (Caution! Extreme fire hazard.) The solvent was evaporated and coevaporated with toluene. The crude product was purified by column chromatography (7:3:1 EtOAc–MeOH–H_2O) to give the title compound **13** as a white foam (75 mg, 84%). $[\alpha]_D$ −19° (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD): δ 4.58 (1H, ddd, $J_{1a,2}$ 3.7, $J_{2,3}$ 3.2 Hz, H-2), 4.38 (1H, dd, $J_{2,3} = J_{3,4} = 3.2$ Hz, H-3), 4.31 (1H, ddd, $J_{2',3'}$ 7.6, $J_{1'a,2'}$ 2.9 Hz, H-2′), 4.27 (1H, ddd, $J_{2',3'}$ 7.6, $J_{3',4'a}$ 3.4, $J_{3',4'b}$ 3.2 Hz, H-3′), 4.05 (1H, ddd, H-5), 4.02 (1H, dd, $J_{4,5}$ 6.9, $J_{3,4}$ 2.7 Hz, H-4), 3.97 (1H, dd, $J_{1'a,1'b}$ 13.4, $J_{1'a,2'}$ 2.9 Hz, H-1′a), 3.93 (1H, dd, $J_{4'a,4'b}$ 12.2, $J_{3',4'a}$ 3.4 Hz, H-4′a), 3.82 (1H, dd, $J_{4'a,4'b}$ 12.2, $J_{3',4'b}$ 3.2 Hz, H-4′b), 3.82–3.75 (2H, m, H-1a, H-1′b), 3.74 (1H, dd, $J_{6a,6b}$ 11.4, $J_{5,6a}$ 3.4 Hz, H-6a), 3.70 (1H, dd, $J_{6a,6b}$ 11.4, $J_{5,6b}$ 3.7 Hz, H-6b), 3.67 (1H, dd, $J_{1a,1b}$ 13.1, $J_{1a,2}$ 3.7 Hz, H-1b); ^{13}C NMR (CD_3OD): δ 81.10 (C-3′), 79.96 (C-3), 78.47 (C-2), 73.01 (C-4), 70.66 (C-5), 68.05 (C-2′), 65.45 (C-6), 61.65 (C-4′), 51.75 (C-1′), 49.79 (C-1); HRMS calcd for $C_{10}H_{20}O_{10}S_2$ (M+H): 365.0576. Found: 365.0570.

3.8. 1,4-Anhydro-4-[(*R*)-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]sulfoniumylidene]-D-galactitol inner salt 14

Compound **11** (130 mg, 0.16 mmol) in 80% AcOH (5 mL) containing $Pd(OH)_2$/C (80 mg) was treated as described for the case of **10**. The title compound **14** was obtained as a white foam (56 mg, 96%). $[\alpha]_D$ +48° (*c* 0.7, MeOH); ^{1}H NMR (D_2O): δ 4.68 (1H, ddd, $J_{1b,2}$ 5.0, $J_{2,3}$ 4.4 Hz, H-2), 4.43 (1H, dd, $J_{2,3} = J_{3,4} = 4.4$ Hz, H-3), 4.36 (1H, ddd, $J_{1'b,2'}$ 8.8, $J_{2',3'}$ 7.2, $J_{1'a,2'}$ 3.3 Hz, H-2′), 4.33 (1H, ddd, $J_{2',3'}$ 7.2, $J_{3',4'a}$ 3.3 Hz, H-3′), 4.17 (1H, m, H-5), 4.10 (1H, dd, $J_{4,5}$ 6.6 Hz, H-4), 3.95 (1H, dd, $J_{4'a,4'b}$ 12.7, $J_{3',4'a}$ 3.3 Hz, H-4′a), 3.93 (1H, dd, $J_{1'a,1'b}$ 13.7, $J_{1'a,2'}$ 3.3 Hz, H-1′a), 3.84 (1H, dd, $J_{4'a,4'b}$ 12.7 Hz, H-4′b), 3.83 (1H, dd, $J_{6a,6b}$ 12.7 Hz, H-6a), 3.81 (1H, dd, $J_{1a,1b}$ 13.2 Hz, H-1a), 3.78 (1H, dd, $J_{1'b,2'}$ 8.8 Hz, H-1′b), 3.71 (1H, dd, $J_{6a,6b}$ 12.7 Hz, H-6b), 3.68 (1H, dd, $J_{1a,1b}$ 13.2 Hz, H-1b); ^{13}C NMR (D_2O): δ 83.08 (C-3′), 80.57 (C-3), 78.53 (C-2), 71.55 (C-4), 71.39 (C-5), 68.26 (C-2′), 66.29 (C-6), 62.05 (C-4′), 51.24 (C-1′), 47.23 (C-1); MALDI-TOF MS: *m/e* 365.02 (M+H); HRMS calcd for $C_{10}H_{20}O_{10}S_2$ (M+H): 365.0576. Found: 365.0569.

Supplementary Data

This paper contains nine pages of Supplementary Data that can be accessed via the web version of this paper.

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